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10/519,132	09/14/2005	Stephen Strittmatter	8155USO1	7561

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EXAMINER	
DUTT, ADITI	

ART UNIT	PAPER NUMBER
1649	

NOTIFICATION DATE	DELIVERY MODE
06/23/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents_Abbott_Park@abbott.com
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Office Action Summary	Application No.	Applicant(s)	
	10/519,132	STRITTMATTER ET AL.	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 2* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 31 March 2009 has been entered.

Status of Claims

2. The amendment filed on 31 March 2009 has been entered into the record and has been fully considered.

3. Claims 1 and 2 are amended. Claims 3-17 are canceled. Please note that claim 17 is missing from the amended claim listing.

4. Claims 1 and 2, directed to a method for identifying an agent which modulates the binding of an RGM (repulsive guidance molecule) to a Neogenin, comprising detecting and monitoring the binding, are being considered for examination in the instant application.

Response to Amendment

Withdrawn objections and/or rejections

5. Upon consideration of the Applicant's amendment, all claim objections and rejections, not reiterated herein have been withdrawn, as overcome by cancellation and/or amendment of claims (31 March 2009).

Specification

6. The amendment dated 31 March 2009 to the disclosure is objected to because of the following informalities:

The Brief description of Figure 1 has the following typographical errors:

1(B) states "RGM-A" instead of "RGM-AP".

1(D) states "200 pM" instead of "230 pM".

1(E) does not describe Figures 1E', 1E" and 1E"' (as labeled in the drawing) on an individual basis.

Appropriate correction is required.

Claim Objections

7. Claim 2 is objected to because of the following informalities:

Claim 2 has a typographical error on line 7 that states "for at time" (emphasis added).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

9. Claim 1 is rejected because the phrase "isolated mammalian RGM and an isolated mammalian Neogenin, having an amino acid sequence of at least 70% identity to SEQ ID NO: 5" is not clear. It is not ascertainable whether the reference of 70% identity to SEQ ID NO: 5 is directed to RGM or to Neogenin, or it is a third component in the recited "mixture". Since the specification does not provide any sequence identifier for RGM, nor does it provide any information on SEQ ID NO: 5, the limitation is vague and unclear.

10. Claim 2 is rejected as being indefinite, because it recites "SEQ ID NO: 5" as corresponding to the amino acid sequence of Neogenin. As SEQ ID NO: 5 is not taught in the instant specification as corresponding to Neogenin, the claim would read on an infinite number of sequences of "a Neogenin" comprising variants and homologues of Neogenin.

It is noted that the instant specification teaches the amino acid sequence of Neogenin as corresponding to SEQ ID NO: 1 (page 11, line 23; Figure 5). Since the limitation of "SEQ ID NO: 5" in the instant claims is directed to

Neogenin amino acid sequence, and since this sequence identifier is absent in the instant disclosure, Examiner will consider the recited sequence identifier as SEQ ID NO: 1 for purpose of examination of the instant application.

Applicant's Remarks

11. Applicant states that claims 1 and 2 have been amended to recite that the Neogenin has an "amino acid sequence of at least 70% identity of SEQ ID NO: 5". Applicant requests the withdrawal of rejection in view of this amendment.

12. Applicant's arguments have been fully considered but not found to be persuasive. Although Applicant has amended the claims to define Neogenin with SEQ ID NO: 5, as stated above this identifier does not define Neogenin. It is suggested that the appropriate sequence identifier should be recited for proper consideration.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1 and 2 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying an agent which

modulates the binding of full-length RGM A or RGM B or amino acids 28-403 of chick RGM to full-length Neogenin, wherein Neogenin corresponds to amino acid sequence of SEQ ID NO: 1 or a soluble ectodomain of chick Neogenin (amino acids 1-1027), and a method for monitoring the specific binding of the above molecules of RGMA/RGMB to Neogenin, does not reasonably provide enablement for the identification of an agent that modulates the binding of RGM A or RGM B to any sequence comprising splice variants or homologues of Neogenin or having at least 70% identity to the amino acid sequence of SEQ ID NO: 1 of Neogenin. Likewise the specification is not enabled for a method for monitoring the binding of RGM A or RGM B to homologues of variants of Neogenin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

14. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, include the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

15. The claims are drawn to a method for identifying an agent which modulates the binding of RGM A or RGM B to a Neogenin, comprising incubating

a mixture of an isolated mammalian (human) RGM and an isolated mammalian (human) Neogenin in the presence of an agent, and detecting the specific binding between RGM A or RGM B and Neogenin, wherein Neogenin has an amino acid sequence of at least 70% identity to SEQ ID NO: 5, wherein a difference in binding in the presence or absence of the agent, will indicate that the agent modulates the binding. Claim 2 further recites that a reduction in the enzymatic signal indicates a reduction in the binding due to an interaction with a specific RGM A or RGM B antibody or a small molecule. It is to be noted that since the limitation of "SEQ ID NO: 5" in claims 1 and 2 is directed to Neogenin amino acid sequence, and since this sequence identifier is absent in the instant disclosure, Examiner interprets the claim as reciting the sequence identifier for Neogenin amino acid sequence as SEQ ID NO: 1 (see instant specification, page 11, line 23; Figure 5), for examination purpose. Also, based on the teachings in the instant disclosure, "at least 70% identity" is broadly interpreted as encompassing any splice variant, homolog of Neogenin.

16. The specification of the instant application teaches that RGM is a 33/35 kDa molecule that is active during vertebrate nervous system development (page 2, para 2; page 14, para 2). The specification also identifies Neogenin, having a sequence homology with the Netrin receptor, Deleted in colorectal cancer (DCC), as a specific receptor for RGM (page 5, para 2-3). Still further, the specification teaches that the mouse genome has 3 RGM related sequences, mRGM-A, mRGM-B and mRGM-C, sharing a 41-49% identity with each other, RGM-A

sharing a 80% identity with chick or cRGM. Furthermore, RGM-A and RGM-B are expressed in various regions of the developing mouse brain and bind to the Neogenin receptor (page 12, para 2; Figure 1E). The specification further teaches that both RGM and Neogenin are highly expressed in the adult nervous system as well as in the injured nervous system, thus implying a role in the adult neural regeneration (page 14, para 2). The specification demonstrates RGM binding sites in the brain by expressing a fusion protein comprising RGM-A fused to human placental alkaline phosphatase (AP) in HEK293 cells (page 12, para 1). Examples 1 and 2 of the instant specification demonstrates the binding of RGA and Neogenin, using the soluble ectodomain of chick Neogenin-1 (amino acid residues 1-1027), and recombinant RGM-AP having amino acid residues 28-403 of chick RGM. However, the specification does not teach any methods or working examples to indicate that RGM A/RGM B will bind to any Neogenin molecule, and further to identify an agent that will modulate the binding such molecules. Undue experimentation would be required of a skilled artisan to determine such.

17. Relevant literature teaches that RGM, a membrane bound glycosylphosphatidylinositol (GPI)-anchored glycoprotein, is an axon guidance molecule consisting of 3 homologues in vertebrates, RGMa, RGMb and RGMc, with RGMa and RGMb showing abundant expression in the early stages of development of the mouse CNS (Yamashita et al. Curr Opin Neurobiol 17: 29-34, 2007; pages 29-30). The art further teaches that RGM binds to a Netrin binding protein, Neogenin, with a higher affinity than that exhibited by Netrin (Yamashita

et al. page 30), the RGM-Neogenin interaction resulting in axon repulsion (Rajagopalan et al. Nat Cell Biol 6: 756-762, 2004, page 761, last para). However, neither the instant specification nor the prior or post art teach that RGM-A or RGM-B can bind to any domain of Neogenin, wherein Neogenin comprises any splice variant or homologue of the amino acid sequence of Neogenin or SEQ ID NO: 1. The specification also does not teach that all possible Neogenin peptides having at least 70% identity with the Neogenin sequence will comprise a domain for specific binding to RGM A or RGM B. There is no guidance to indicate specific amino acid residues and other sequences that would be critical for specific binding between RGM and Neogenin. Thus, undue experimentation would be required of the skilled artisan to identify the precise structural characteristics of all variants and homologues of Neogenin retaining specific binding activity with RGM A or RGM B.

18. Furthermore, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active

sites. These or other regions may also be critical determinants of RGM-Neogenin binding activity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the cell membrane permeable peptides which are tolerant to change (e.g. such as by amino acid substitutions), and the nature and extent of changes that can be made in these positions. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

19. Hence, the state of prior and post art do not enable a method to monitor the specific binding of RGM A or RGM B sequence to any splice variant or

homolog of Neogenin, or a method to identify an agent which modulates the specific binding of RGM to any Neogenin. In the absence of guidance with regards to such binding and the effectiveness of identifying an agent that will modulate the binding of these molecules with a reasonable amount of success, undue experimentation would be required of a skilled artisan. The specification must provide such guidance commensurate in scope with the claims.

20. Due to the large quantity of experimentation necessary to identify an agent which modulates the binding of RGMA/B molecule to any variant or homolog of Neogenin, wherein the sequence of the Neogenin peptide is at least 70% of full length Neogenin, and monitor such binding, the lack of direction/guidance presented in the specification; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of the effects of substitution on protein structure and function; and the breadth of the claims which fail to recite any structural or functional limitations of Neogenin with respect to specific binding with RGM, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Applicant's Remarks

21. Applicant argues that claims 1 and 2 have been amended to limit RGM to RGM A or RGM B. In view of such amendment, Applicant requests the withdrawal of the rejection.

22. Applicant's arguments have been fully considered but found to be persuasive in part. The amendment limiting RGM molecule to RGM A or RGM B, results in the withdrawal of the rejection with respect to the different RGM sequences. However, the claims broadly read on any Neogenin sequence that is at least 70% identical to the Neogenin sequence of SEQ ID NO: 1. A skilled artisan would not be able to make and use the claimed invention as broadly claimed for reasons explained above.

Claim Rejections - 35 USC § 112, first paragraph- Written Description

23. Claims 1 and 2 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

24. The claims are drawn to a method for identifying an agent which modulates the binding of RGM A or RGM B to a Neogenin, comprising incubating a mixture of an isolated mammalian (human) RGM and an isolated mammalian (human) Neogenin in the presence of an agent, and detecting the specific binding between RGM A or RGM B and Neogenin, wherein Neogenin has an amino acid sequence of at least 70% identity to SEQ ID NO: 5, wherein a difference in binding in the presence or absence of the agent, will indicate that

the agent modulates the binding. Claim 2 further recites that a reduction in the enzymatic signal indicates a reduction in the binding due to an interaction with a specific RGM A or RGM B antibody or a small molecule. It is to be noted that since the limitation of "SEQ ID NO: 5" in claims 1 and 2 is directed to Neogenin amino acid sequence, and since this sequence identifier is absent in the instant disclosure, Examiner interprets the claim as reciting the sequence identifier for Neogenin amino acid sequence as SEQ ID NO: 1 (see instant specification, page 11, line 23; Figure 5), for examination purpose. Also, based on the teachings in the instant disclosure, "at least 70% identity" is broadly interpreted as encompassing any splice variant, homolog of Neogenin.

25. The specification of the instant application teaches that RGM is a 33/35 kDa molecule that is active during vertebrate nervous system development (page 2, para 2; page 14, para 2). The specification also identifies Neogenin, having a sequence homology with the Netrin receptor, Deleted in colorectal cancer (DCC), as a specific receptor for RGM (page 5, para 2-3). Still further, the specification teaches that the mouse genome has 3 RGM related sequences, mRGM-A, mRGM-B and mRGM-C, sharing a 41-49% identity with each other, RGM-A sharing a 80% identity with chick or cRGM. Furthermore, RGM-A and RGM-B are expressed in various regions of the developing mouse brain and bind to the Neogenin receptor (page 12, para 2; Figure 1E). The specification further teaches that both RGM and Neogenin are highly expressed in the adult nervous system as well as in the injured nervous system, thus implying a role in the adult

neural regeneration (page 14, para 2). The specification demonstrates RGM binding sites in the brain by expressing a fusion protein comprising RGM-A fused to human placental alkaline phosphatase (AP) in HEK293 cells (page 12, para 1). Examples 1 and 2 of the instant specification demonstrates the binding of RGA and Neogenin, using the soluble ectodomain of chick Neogenin-1 (amino acid residues 1-1027), and recombinant RGM-AP having amino acid residues 28-403 of chick RGM. However, the claims do not require that the amino acid sequence of Neogenin has any particular conserved structure. Thus, the claims are drawn to a genus of polypeptide sequences, representing a genus of variants and homologues of Neogenin.

26. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. The specification has not shown a relationship between the structure, function, or properties of the claimed genus of polypeptides and mutant polypeptides. There is not even identification of any particular portion of the Neogenin peptide structure or function that must be conserved, or particular amino acids that can be substituted or deleted without affecting the specific binding with RGM A or RGM B. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the

specification does not provide adequate written description of the claimed genus. The brief description in the specification of one Neogenin peptide (SEQ ID NO.: 1) and one soluble ectodomain of Neogenin-1 (amino acids 1-1027), that specifically bind to full-length RGM A or RGM B, or amino acid residues 28-403 of chick RGM, is not adequate written description of an entire genus of functionally equivalent Neogenin polypeptides, which incorporate all variants, and homologues thereof.

27. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

28. With the exception of wild type Neogenin of SEQ ID NO: 1 and amino acids 1-1027 of chick Neogenin, demonstrating specific binding with full-length RGM A, RGM B or amino acids 28-403 of chick RGM, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or production. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The

polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

29. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class.

30. Therefore, wild type Neogenin of SEQ ID NO: 1, and amino acids 1-1027 of chick Neogenin, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Conclusion

31. No claims are allowed.

32. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

33. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on (571) 272-0911. The

fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

34. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
16 June 2009

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649